AD_____
(Leave blank)

Award Number:
W81XWH-08-2-0061

TITLE:
"Advanced MRI in Blast-Related TBI"

PRINCIPAL INVESTIGATOR:
David L. Brody, MD PhD

CONTRACTING ORGANIZATION:
Washington University
St Louis MO 63110,

REPORT DATE:
September 2010

TYPE OF REPORT:
Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT:

Approved for public release; distribution unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE *(DD-MM-YYYY)*	**2. REPORT TYPE**	**3. DATES COVERED** *(From - To)*
30-Sep-2010	Annual	01 SEP 2008 - 1 AUG 2010

4. TITLE AND SUBTITLE

Advanced MRI in Blast-Related TBI

5a. CONTRACT NUMBER
W81XWH-08-2-0061

5b. GRANT NUMBER
PT075299

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

David L. Brody

brodyd@neuro.wustl.edu

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Washington University,
660 S Euclid Ave Box
8111, St Louis MO 63110,

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for public release; distribution unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

The purpose of the research effort is to test two advanced MRI methods, DTI and resting-state fMRI, in active-duty military blast-related TBI patients acutely after injury and correlate findings with TBI-related clinical outcomes 6-12 months later. These methods may add clinically useful predictive information following traumatic brain injury that could be of assistance in standardizing diagnostic criteria for TBI, making return-to-duty triage decisions, guiding post-injury rehabilitation, and developing novel therapeutics. The overarching hypothesis guiding this project is that traumatic axonal injury is a principal cause of impaired brain function following blast-related TBI. The major findings as of 1 Aug 2010 are as follows:

1) 63 blast-related TBI patients and 21 controls have been enrolled. MRI scans have been successful with no adverse events.
2) Analyses of initial scans have revealed abnormalities on DTI indicative of traumatic axonal injury in 20/63 injured subjects that were not detectible on conventional MRI or CT.
3) Abnormalities were detected in regions of the brain predicted to be vulnerable to blast, but not typically injured in civilian TBI.
4) At follow-up, post-traumatic stress disorder was common, and its severity could be partially predicted by specific DTI abnormalities. This raises the possibility that injury to specific brain regions may impair emotional processing.

15. SUBJECT TERMS
Traumatic Brain Injury. Blast. MRI. Diffusion Tensor Imaging.

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**			USAMRMC
u	u	u	uu	11	**19b. TELEPHONE NUMBER** *(include area code)*

Table of Contents

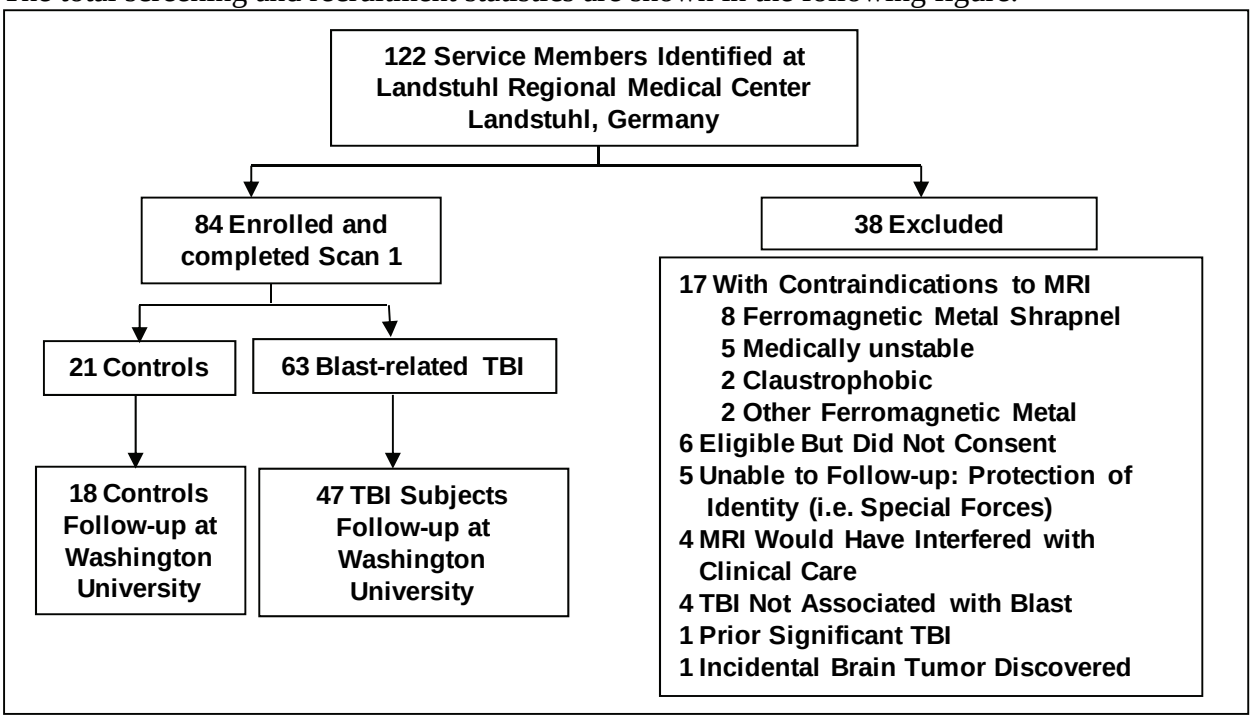
Page

Introduction:
The purpose of the research effort is to test two advanced MRI methods- DTI and resting-state fMRI- in active-duty military blast-related TBI patients acutely after injury and correlate findings with TBI-related clinical outcomes 6-12 months later. These methods may add clinically useful predictive information following traumatic brain injury that could be of assistance in standardizing diagnostic criteria for TBI, making return-to-duty triage decisions, guiding post-injury rehabilitation, and developing novel therapeutics. The overarching hypothesis guiding this project is that traumatic axonal injury is a principal cause of impaired brain function following blast-related TBI.

Body:
The research accomplishments associated with the tasks outlined in the Statement of Work as follows.

Task 1) to obtain DTI, resting-state fMRI and conventional MRI scans acutely after injury at Landstuhl Regional Medical Center (LRMC) on a total of 100 military personnel, 80 who have sustained blast-related TBI and 20 who have sustained other injuries, but have no evidence of TBI.

A total of 122 active duty US military personnel were screened at LRMC. In total, 84 subjects provided written informed consent and were enrolled in the study; 63 had sustained acute blast-related TBI and 21 had blast exposure, sustained other injuries but have no evidence of TBI. All participants have been screened carefully for contraindications to MRI. High quality DTI, resting-state fMRI and conventional MRI scans have been acquired in all subjects. There have been no adverse events resulting from the scans.
The total screening and recruitment statistics are shown in the following figure.



We have obtained supplementary funding to recruit an additional 40 blast-related TBI subjects for this study, which will now extend an additional 9 months. Human studies permissions to increase the number of participants have been obtained from Washington University and Brooke Army Medical Center (which oversees LRMC).

DTI revealed abnormalities after blast-related TBI that are not apparent on conventional MRI (Fig 2). These were found both in regions commonly injured in civilian TBI (Fig. 3A) and in regions predicted to be vulnerable to blast, but not commonly injured in mild civilian TBI (Fig. 3B)

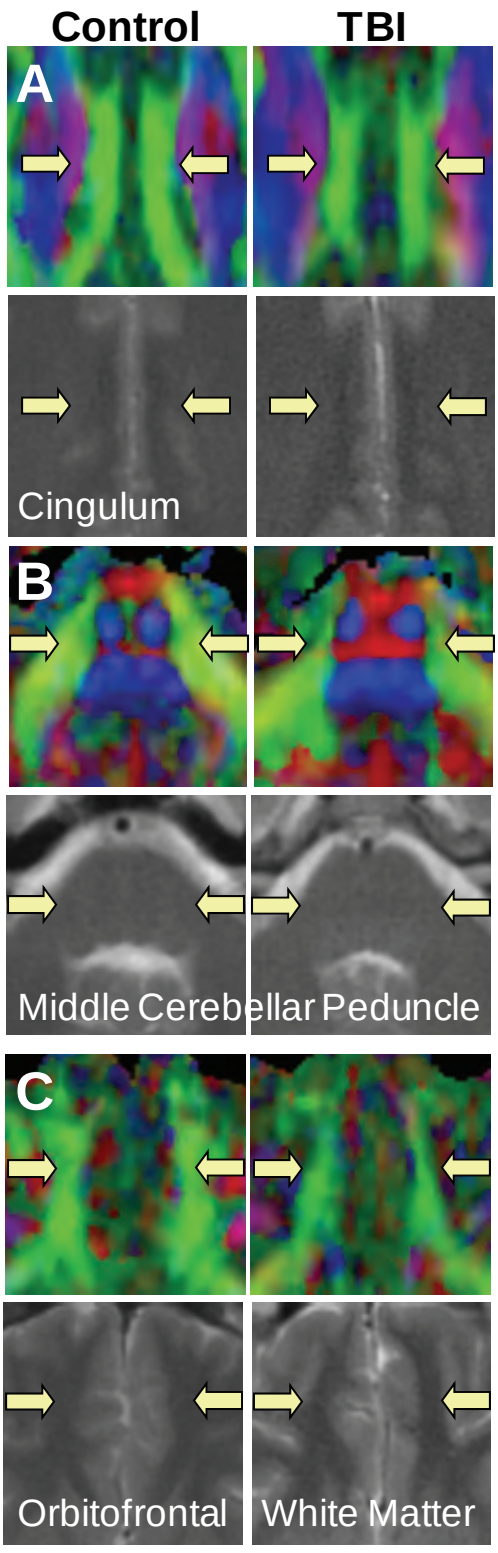


Figure 2: DTI reveals abnormalities after blast-related TBI that are not apparent on conventional MRI. Top panels: DTI relative anisotropy maps. Colors indicate principal diffusion directions: red = right-left, green = anterior-posterior, blue = dorsal-ventral. Brighter colors indicate higher relative anisotropy. Arrows indicate regions with abnormally low relative anisotropy on DTI in the TBI subjects compared with controls. Bottom panels: conventional T2-weighted MRI showing no detectible abnormalities at the same locations in the same subjects. Small differences in the appearance of the T2 weighted images are due to normal subject-to-subject variability. **A.** Cingulum bundles. **B.** Middle cerebellar peduncles. **C.** Orbitofrontal white matter.

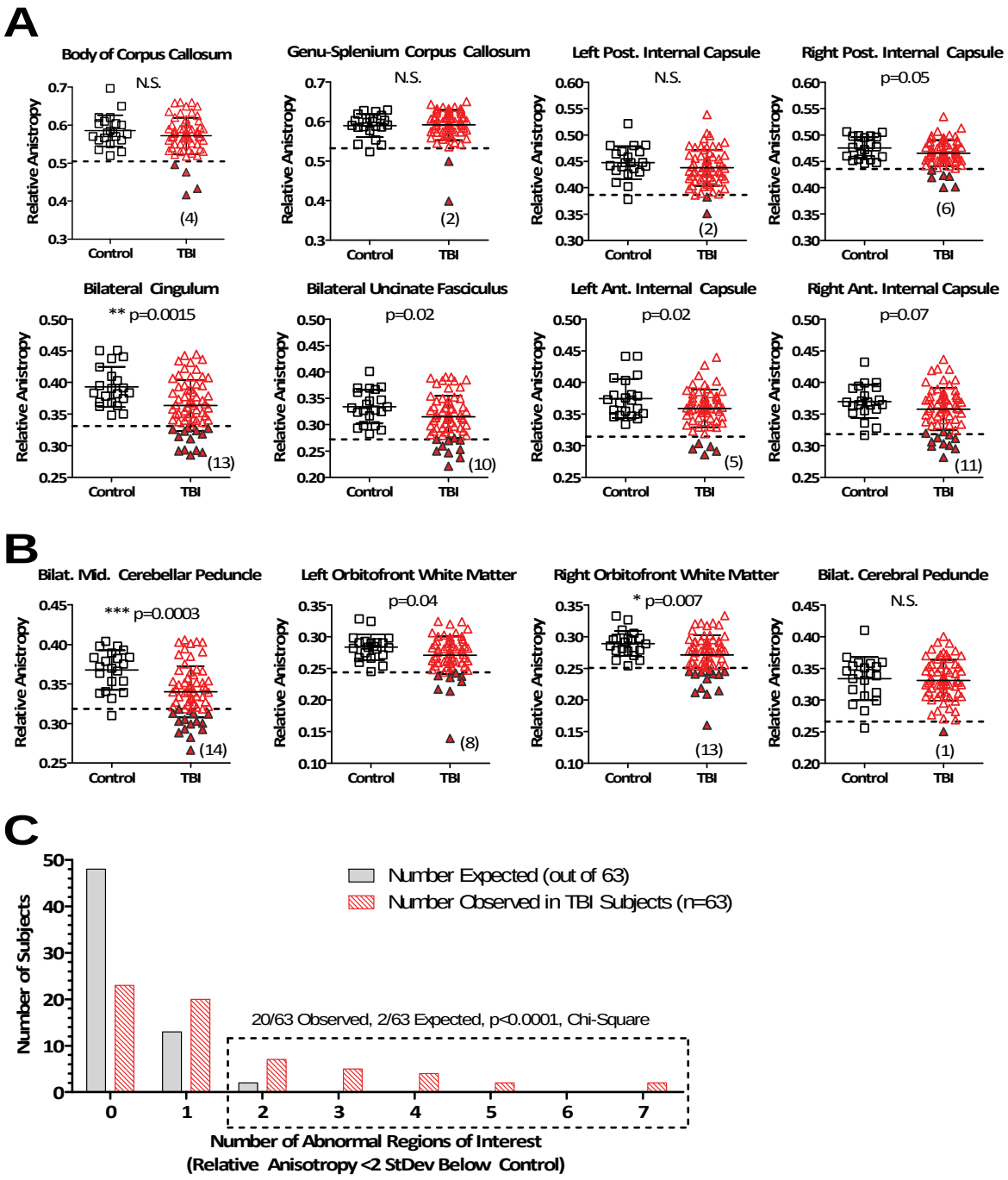


Figure 3: DTI abnormalities in blast-related TBI subjects. **A.** Scatter plots of relative anisotropy in brain regions commonly injured in civilian TBI. P-values indicate 1-sided t-tests. N.S. Not significant. Bars indicated means and standard deviations. Dashed lines indicate 2 standard deviations below the mean of the control group. Numbers in parentheses indicate the number TBI subjects with relative anisotropy below this cutoff. **B.** Scatter plots of relative anisotropy in brain regions predicted to be vulnerable to blast, but not commonly affected in civilian TBI. **C.** Observed numbers of DTI abnormalities in individual TBI subjects vs. numbers expected by chance.

Task 2) to collect detailed clinical information on TBI-related outcomes 6-12 months after injury on the same participants recruited for Task 1. This will include global outcome assessments, neuropsychological testing for memory, attention and executive function deficits, motor performance measures, and clinician administered rating scales for depression and post-traumatic stress disorder. Repeat DTI, resting-state fMRI and conventional MRI will be performed to track the evolution of the injuries.

We have completed a total of 65 evaluations. There have been no complications or adverse events to date in this phase. Our clinical coordinator, Ms. Anne Johnson, at Washington University has provided logistics. Reasons for inability of 19 subjects (3 controls and 16 with TBI) to follow-up at Washington University included inability or unwillingness to travel to St. Louis (10 subjects), withdrawal of consent (4 subjects), inability to maintain telephone or email contact (2 subjects), severe psychiatric illness (1 subject), redeployment overseas (1 subject), and other severe illness (1 subject).

Follow-up MRI scans demonstrated that the DTI characteristics evolved over time (Fig. 4). Conventional MRI was normal in all follow-up MRI scans.

Clinical assessments performed 6-12 months after injury revealed that more TBI subjects (41/47, 87%) than controls (11/18, 61%) had moderate to severe overall disability, defined as Glasgow Outcome Scale-Extended scores of 6 or less ($p=0.019$, Chi-square). Neuropsychological test results did not indicate substantial differences between the TBI subjects and the controls; both groups generally performed within expectation for age and educational level . This is consistent with previous reports in blast-related “mild” TBI subjects.25,26 Standardized neurological assessments similarly did not reveal major abnormalities, though TBI subjects were slightly more impaired than controls. Subjects who completed in-person clinical assessments were similar to those who were not available for follow-up.

Psychiatric assessments revealed substantially more frequent and more severe PTSD in the TBI subjects. Specifically, 61% (29/47) of TBI subjects and 28% (5/18) of controls met DSM-IV criteria for PTSD ($p=0.0143$, Chi-square) as assessed using the CAPS. The severity of PTSD was also significantly greater in the TBI group ($p=0.004$, t-test).

PTSD was strongly associated with overall adverse outcomes. Across both TBI and control groups, 33/34 (97%) of subjects that met all criteria for PTSD had moderate to severe overall disability vs. 19/31 (61%) that did not meet full PTSD criteria ($p=0.0003$, Chi-square). A similar relationship held for the TBI subjects in isolation (28/29 vs. 13/19, $p=0.015$). CAPS scores were 62 ± 25 in subjects with moderate to severe disability vs. 31 ± 24 in subjects with good outcomes ($p=0.0001$, t-test).

Depression also played a role in overall outcomes, but did not differentiate strongly between TBI and control subjects

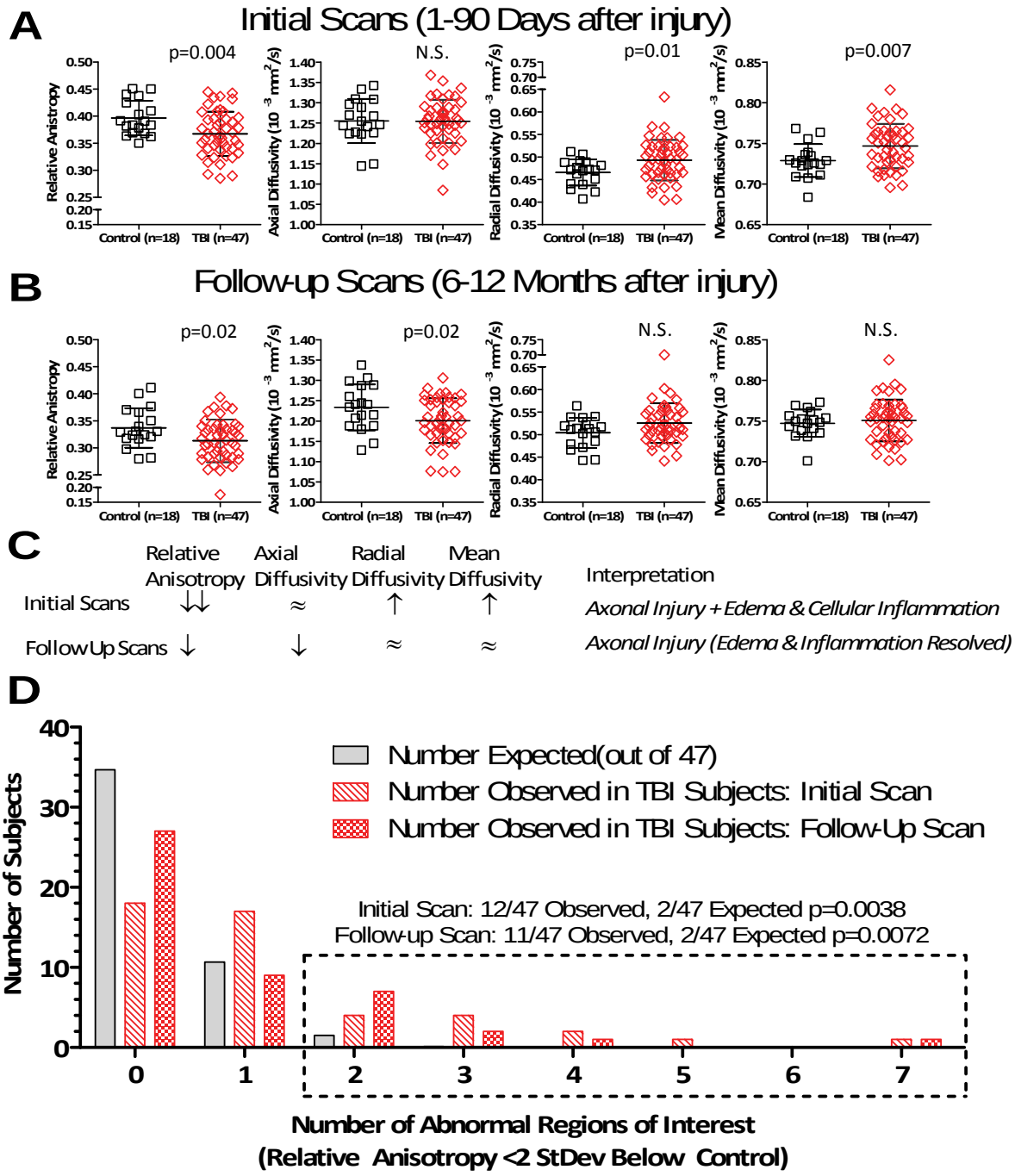


Figure 4: Evolution of DTI parameter abnormalities over time. Data shown for bilateral cingulum bundles. **A.** Initial scans indicated reduced relative anisotropy, increased radial diffusivity and increased mean diffusivity. **B.** Follow-up scans indicated reduced relative anisotropy and reduced axial diffusivity. **C.** Interpretation of changes in DTI parameters. **D.** Observed vs. expected numbers of DTI abnormalities in the same 47 individual TBI subjects at initial scans and follow-up scans.

Task 3) to extensively analyze the acute imaging predictors and correlates of 6-12 month clinical outcomes. Several prespecified hypotheses based on known brain anatomical-clinical correlations will be tested. Also, exploratory approaches will be used as the structural bases for many post-traumatic deficits and disorders are not well understood.

We tested the hypothesis that specific DTI abnormalities could help predict PTSD severity. Univariate DTI predictors of CAPS scores included relative anisotropy in the left posterior limb of the internal capsule (r= -0.29, p=0.021), the right posterior limb of the internal capsule (r= -0.28, p=0.025), the right orbitofrontal white matter (r= -0.27, p=0.032), and the right cingulum bundle (r= -0.22, p=0.072). The mean relative anisotropy across these 4 white matter regions was a stronger predictor of CAPS score than any single region (Fig. 4C, r= -0.39, p=0.001). The direction of the correlations indicated that lower (more abnormal) relative anisotropy was associated with higher (more severe) CAPS scores. In addition, lower educational achievement correlated with higher CAPS score (Spearman r= -0.29, $p<0.05$) as did poor performance on the Military Acute Concussion Evaluation (MACE) at LRMC (p= 0.03, 1-sided t-test).

A generalized linear model incorporating these early clinical factors and DTI abnormalities significantly predicted PTSD severity. The model included the clinical diagnosis of TBI vs. control and MACE score <22 as dichotomous variables, plus years of education and mean relative anisotropy across the 4 white matter regions described above as continuous variables. Importantly, this model incorporated only information obtained at LRMC 1-90 days after injury. Predicted CAPS scores correlated moderately well with observed CAPS scores (r= 0.55, p=0.0002). DTI data significantly added to the strength of the correlation (β_{DTI}= -0.28, p=0.016), whereas after including the DTI data, both the clinical diagnosis of TBI (p=0.14) and poor MACE performance (p=0.05) were less significantly associated with PTSD severity. The model performed similarly in the TBI patients alone (r=0.49, p=0.008, β_{DTI}= -0.30, p=0.03). Using a split sample approach, model parameters derived using half of the TBI subjects and half of the controls significantly predicted the PTSD severity in the other half (r=0.48, p=0.005) with no additional free parameters.

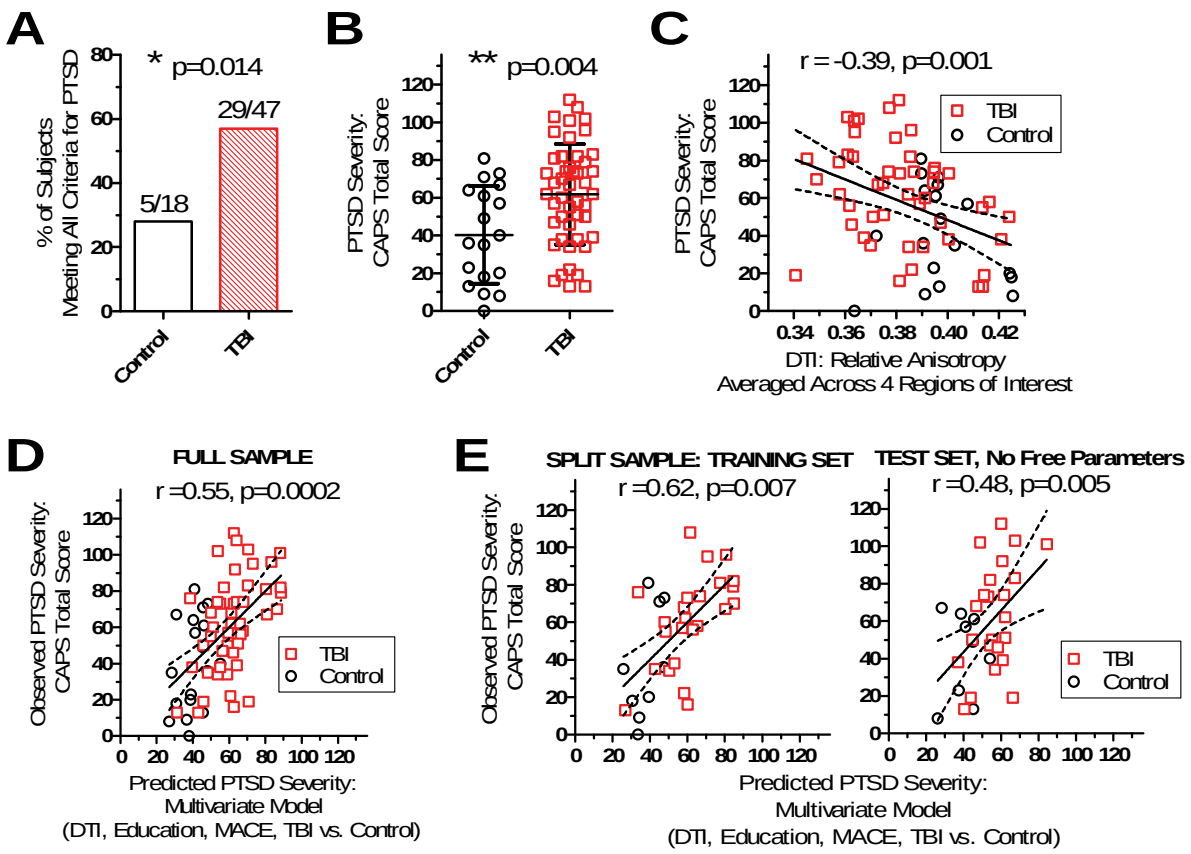


Figure 5: PTSD in TBI and control subjects; relationship to DTI abnormalities. **A.** Number of subjects meeting all DSM-IV criteria for PTSD. **B.** Severity of PTSD as assessed by CAPS total score (range 0-136, higher scores worse). **C.** PTSD severity 6-12 months after injury vs. DTI relative anisotropy measurements 1-90 days after injury. Relative anisotropy averaged across 4 regions of interest: right orbitofrontal white matter, right cingulum, right posterior limb of the internal capsule and left posterior limb of the internal capsule. **D.** Multivariate predictive model of PTSD severity based on early DTI and clinical data. DTI data significantly added to the correlation strength (β_{DTI}= -0.28, p=0.016). **E.** Split sample validation of the multivariate model.

Key Research Accomplishments:

- A total of 84 subjects have been enrolled at Landstuhl Regional Medical Center, including 64 blast-related TBI patients and 21 controls. All acute MRI scans have been performed successfully with no adverse events.
- Analyses of initial scans have revealed abnormalities on DTI indicative of traumatic axonal injury in injured subjects that were not detectible on conventional MRI or CT.
- Many of these abnormalities were found in regions not commonly injured in civilian TBI, but predicted to be especially vulnerable to blast injuries.
- 65 clinical outcome evaluations and repeat scans have been performed at Washington University with no adverse events.
- DTI abnormalities were found to evolve from the time of initial scans to the time of follow-up scans. This evolution proceeded in a manner that is consistent with resolution of edema and inflammation but persistent axonal injury.
- Cognitive performance was found to be generally intact in the TBI subjects, and none had persistent focal neurological deficits at follow-up.
- Post-traumatic stress disorder was found to be more common and more severe in the TBI subjects than the control subjects.
- Initial analyses have revealed that DTI abnormalities in specific brain regions correlate with the severity of post-traumatic stress disorder.

Reportable Outcomes:

Abstracts:

Dr. Mac Donald presented aspects of these results at the 2010 International Society for Magnetic Resonance in Medicine (ISMRM) meeting.

Dr. Brody presented aspects of these results at the 2010 Advanced Technology Applications for Combat Casualty Care (ATACCC) meeting.

Conclusion: An advanced MRI study of acute blast-related TBI in US military personnel is feasible. These advanced MRI methods have demonstrated abnormalities indicative of traumatic axonal injury that were not detected using standard MRI or CT. This approach, if successful, has the potential to dramatically advance the acute assessment of patients with blast-related TBI, and may generalize to other injury mechanisms as well. In a military setting, it may allow improved triage / return-to-duty decisions to be made, and provide early guidance with regard to appropriate rehabilitative strategies.

References:

None.

Appendices:

None.